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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/874,166	06/04/2001	William Thomas Melvin	12489-003002/UMMC Ref: UM	8129

26161 7590 03/10/2004

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/874,166	MELVIN ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-40* is/are pending in the application.

4a) Of the above claim(s) *36-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09043814.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This Action is in response to the communication filed on 11/6/03. Claims 27-40 are currently pending in the application and are addressed herein.

Election/Restrictions

2. Applicant's election without traverse of Group I (claims 27-35) in the Paper filed 11/6/03 is acknowledged.

3. Claims 36-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the Paper filed 11/6/03.

4. Claims 27-35 are examined herein.

Claim Rejections - 35 USC § 112, second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 27, 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 27 is drawn to a method for stimulating the human immune system, the method comprising activating human T cells that recognize a human CYP1B1 epitope. This claim is

indefinite because the claim does not set forth the materials and method steps that result in the activation of the human T cells. Therefore, one of skill in the art would not know what materials to use nor would the skilled artisan know the method steps to perform in order to successfully complete the claimed method.

8. It is noted that claim 28 indicates that the activation of T cells is achieved by immunizing a human with a CYP1B1 amino acid sequence, thus indicating the required material (a CYP1B1 amino acid sequence) and the required method step (immunizing a human) to successfully complete the method of claim 27. Therefore, incorporating the limitations set forth in claim 28 into claim 27 would obviate the rejection of claim 27.

9. Claims 29 and 30 depend on claim 28; however, the instant claims do not set forth a nexus between claim 28 and the instant claims such that it is clear that the activation of cytotoxic T cells (claim 29) and helper T cells (claim 30) is achieved by immunizing a human with a human CYP1B1 epitope. As written, the instant claims (29 and 30) merely indicate that the claims are drawn to the method of claim 28, wherein the method comprises activating cytotoxic T cells (claim 29) and helper T cells (claims 30). There is no definite indication of the materials and method steps by which the activation of cytotoxic and helper T cells is achieved. Therefore, it is unclear if the activation of cytotoxic T cells (claim 29) and the activation of helper T cells (claim 30) is achieved by immunizing a human with a CYP1B1 amino acid sequence or by another means not set forth in the claims.

10. It is noted that amending the claims such that the claims incorporate the limitation "wherein said immunizing a human with a CYP1B1 amino acid sequence activates" cytotoxic T cells (for claim 29) or helper T cells (for claim 30) would obviate this rejection.

Claim Rejections - 35 USC § 112, first paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 27-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

13. The instant claims are drawn to a method for stimulating the human immune system, the method comprising activating human T cells that recognize a human CYP1B1 epitope (see claim 27); wherein activation of T cells is achieved by immunizing a human with a CYP1B1 epitope (claim 28); wherein the method comprises activating cytotoxic T cells (CTLs) (claim 29); wherein the method comprises activating helper T cells (claim 30); wherein the human has cancer (claim 31); wherein the cancer is in the bladder, brain, etc. (see claim 32); wherein the immunization results in a cell mediated or humoral immune response against the cancer (claim 33); and wherein the CYP1B1 amino acid sequence comprises specific sequences, SEQ ID NO. 1 or SEQ ID NO. 2 (claims 34 and 35).

14. Therefore, the claims encompass stimulating the human immune response by activating human T cells that recognize a human CYP1B1 epitope. As written, claim 27 is very broad and encompasses activating human T cells that recognize a human CYP1B1 epitope by any

reasonable method. However, the only method steps described in the specification for activating the human T cells that recognize human CYP1B1 is by administering a CYP1B1 epitope. Considering the breadth of claim 27, the method encompasses administering molecules that can activate human T cells that recognize a human CYP1B1 epitope. This genus of molecules is indefinite in size, but could encompass thousands of different molecules, considering every molecule that could activate human T cells that recognize a human CYP1B1 epitope, including molecules that have yet to be identified. This large genus of molecules can encompass molecules that have completely unrelated chemical structures and functions. For instance, the genus could encompass small organic molecules, nucleic acids, polypeptides, and polypeptide epitopes of CYP1B1.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164)

In the instant case, the specification has described two specific epitopes of CYP1B1 which allegedly can be used to activate human T cells that recognize a human CYP1B1 epitope (SEQ ID NOS: 1 and 2). Considering the broad genus of molecules encompassed by the claims, which includes non-CYP1B1 epitopes as well as CYP1B1 epitopes, the specification has not adequately described representative number of species molecules encompassed by the claims.

With respect to the broadest claims, applicants have not identified any common structural elements that are critical to the function of molecules encompassed by the claims. With respect to the claims that are specifically drawn to CYP1B1 epitopes, it is noted that applicants have identified two CYP1B1 epitopes that stimulate an antibody production in mice. However, the specification has not specifically identified any CYP1B1 epitopes that have been shown to activate human T cells. Therefore, applicants have also not adequately described the CYP1B1 epitopes encompassed by the claims such that one of skill in the art would be able to recognize which CYP1B1 epitopes activate human T cells without performing an undue amount of additional experimentation.

15. Additionally, claims 27-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, in view of the written description rejection above. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

16. Considering that the Applicants have not adequately described that genus of molecules that can activate human T cells that recognize a human CYP1B1 epitope as indicated above), one of skill in the art would not know how to make or use the claimed invention without first performing additional experimentation to identify a representative number of molecules encompassed by the claims. The amount of additional experimentation required is considered undue, in view of the lack of guidance and working examples present in the instant specification.

17. Claims 27-35 are also rejected under 35 U.S.C. 112, first paragraph (in addition to, and separate from the written description rejection above), as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

A mentioned above, the claims are drawn to a method of stimulating the human immune response by activating human T cells that recognize a human CYP1B1 epitope, and include stimulating an immune response against cancer cells in a human having the cancer. Therefore, the claims encompass cancer immunotherapy.

The breadth of the claims

The claims are very broad. The broadest claims encompass stimulating an immune response by activating human T cells that recognize a human CYP1B1 epitope by administering any compound that can activate said human T cells. The claims can also encompass

administering any human CYP1B1 epitope (such as SEQ ID NOS 1 or 2) that activate said human T cells.

The unpredictability of the art and the state of the prior art

However, the state of the art, including the post-filing art indicate that cancer immunotherapy is not a predictable science. Furthermore, the relevant art recognizes a number caveats and obstacles that must be overcome before the cancer immunotherapy methods can be considered a matter a routine experimentation.

For instance, Bodey et al. (2000) teaches: "The cancer vaccine approach to therapy is based on the notion that the immune system could possibly mount a rejection strength response against the neoplastically transformed cell conglomerate. However, due to the low immunogenicity of tumor associated antigens, down regulation of MHC molecules, the lack of adequate co stimulatory molecule expression, secretion of immune inhibitory cytokines, etc., such expectation are rarely fulfilled...faulty antigen presentation which could result in tolerance induction to the antigens contained within the vaccine, and subsequent rapid tumor progression." (Page 2665, column one).

Gouttefangeas et al. (2000) teaches,

> "As most cancer patients obviously do not mount efficient T cell responses against their tumors, the task is clear: immunotherapies must induce cancer-destroying T cells in patients. Although this goal appear straight forward, effective immunotherapy has remained elusive because of three major problems: first, for many tumors, no or not enough suitable antigens are known; second, no consensus exists for the best antigen formulation or the route of immunization; and third, tumors under immune attack tend to be selected for antigen loss variants." (See p. 491, first column).

Thus, Gouttefangeas indicates that patients that have tumors which express the tumor antigen do not mount an efficient immune response to these tumors. Therefore, administering a

human tumor antigen to a human comprising a tumor that expresses the tumor antigen may not be sufficient to activate an immune response to the human tumor antigen. Furthermore, Gouttefangeas indicates that a single tumor antigen may not be sufficient to activate an effective immune response to the tumor; however, in the instant case, the specification has only described epitopes of a single tumor antigen, human CYP1B1. Finally, Gouttefangeas teaches that using immunotherapy for cancer treatment is unpredictable because the treatment can select for tumor cells that do not express the tumor antigen, thus rendering the treatment ineffective against the tumor cells that do not express the antigen.

Radoja et al. (Mol Med 2000; 6:465-79) teaches that cancer-induced defective cytotoxic T lymphocyte is probably another mechanism how tumor antigen escape immune surveillance. Specifically, Radoja teaches,

> "THE NOTION THAT A DEFICIT IN IMMUNE CELL FUNCTIONS PERMITS TUMOR GROWTH HAS RECEIVED EXPERIMENTAL SUPPORT WITH THE DISCOVERY OF SEVERAL DIFFERENT BIOCHEMICAL DEFECTS IN T LYMPHOCYTES THAT INFILTRATE CANCERS" (abstract). "ACCUMULATION OF CIRCULATING ANTITUMOR IMMUNOGLOBULIN G IN CANCER PATIENTS SHOW THAT THE PRIMING PHASE OF ANTITUMOR IMMUNE RESPONSE IS FUNCTIONAL DURING THE RELATIVELY SLOW PROCESS OF NASCENT TUMOR GROWTH...IN BOTH HUMAN CANCER PATIENTS AND RODENTS BEARING TUMORS OF DIFFERENT HISTOLOGIC ORIGIN, SYSTEMIC IMMUNITY IS NOT PROFOUNDLY SUPPRESSED..." "HOWEVER, INHIBITION OF A SPECIFIC ANTITUMOR IMMUNE RESPONSE HAS BEEN OBSERVED FREQUENTLY. A VARIETY OF MECHANISM HAVE BEEN PROPOSED TO ACCOUNT FOR DEFECTIVE ANTITUMOR IMMUNE RESPONSE, INCLUDING: SECRETION OF SUPPRESSIVE FACTORS IN THE TUMOR MICROENVIRONMENT, THE LACK OF EXPRESSION OF COSTIMULATORY SIGNALS ON TUMOR CELLS, INDUCTION OF REGULATORY T CELLS HAVING A SUPPRESSIVE PHENOTYPE, LOSS OF ANTIGEN PRESENTATION FUNCTION IN THE TUMOR, LOSS OF EXPRESSION OF HLA CLASS I ANTIGEN PRESENTING MOLECULES IN TUMORS, TUMOR-INDUCED T-CELL SIGNALING DEFECTS, LOSS OF TUMOR ANTIGEN EXPRESSION, IMMUNOLOGICAL IGNORANCE AND, SINCE MANY TUMOR ANTIGENS ARE EITHER UNMODIFIED SELF OR EPITOPES CLOSELY RELATED TO SELF, THE REDUCTION OF THE REPERTOIRE OF POTENTIAL HIGH AFFINITY ANTITUMOR T-CELL CLONES DURING T-CELL MATURATION IN THE THYMUS" (Introduction).

Thus, it is evident that the skilled artisan, while acknowledging the significant potential of immunotherapy for cancer, still recognizes that such therapy is neither routine nor wholly accepted. Furthermore, significant development and further guidance is necessary for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for the instant methods.

In order to enable the instant claims in light of the state of the relevant art, the applicant must provide guidance/working examples to demonstrate that the CYP1B1 epitopes are highly immunogenic and could provoke a useful immune response without the problems in the cited references or must provide ways to overcome the cited difficulties.

Working Examples and Guidance in the Specification

The specification does not have any working examples that indicate that the disclosed CYP1B1 epitopes (or any CYP1B1 epitopes, for that matter) can be used stimulate a human T cell response. The only examples provided indicate that the human CYP1B1 epitopes disclosed can be used to raise antibodies against the epitopes in mice. However, as indicated above stimulating a human immune response using a human tumor antigen epitope is not a matter of routine experimentation for the reasons indicated.

Quantity of Experimentation

Considering the breadth of the claims, and the unpredictability of cancer immunotherapy recognized in the art, additional experimentation is required I order for one of skill in the art to be able to practice the claimed invention. Considering the lack of working examples or guidance in the specification and also considering the teachings of the relevant art that the required

experimentation is not routine, the amount of additional experimentation required is deemed to be undue.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of cancer immunotherapy recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification, and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (571) 272-0756. The examiner can normally be reached on M-F (8:00-5:30) with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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ART UNIT 1635

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